Topical Review

Muscle-derived interleukin-6: possible biological effects

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Interleukin-6 (IL-6) is produced locally in working skeletal muscle and can account for the increase in plasma IL-6 during exercise. The production of IL-6 during exercise is related to the intensity and duration of the exercise, and low muscle glycogen content stimulates the production. Muscle-derived IL-6 is released into the circulation during exercise in high amounts and is likely to work in a hormone-like fashion, exerting an effect on the liver and adipose tissue, thereby contributing to the maintenance of glucose homeostasis during exercise and mediating exercise-induced lipolysis. Muscle-derived IL-6 may also work to inhibit the effects of pro-inflammatory cytokines such as tumour necrosis factor α. The latter cytokine is produced by adipose tissue and inflammatory cells and appears to play a pathogenetic role in insulin resistance and atherogenesis.

Recent studies show that several cytokines can be detected in plasma during and after strenuous exercise (Pedersen & Hoffman-Goetz, 2000; Pedersen *et al.* 2001). Thus, the increase in tumour necrosis factor (TNF)α and interleukin (IL)-1β levels is accompanied by a dramatic increase in IL-6. This increase is followed by increases in cytokine inhibitors (IL-1 receptor antagonist (IL-1ra), TNF receptors and the anti-inflammatory cytokine IL-10 (Ostrowski *et al.* 1998*a*, *b*, 1999). Also, concentrations of the chemokines, IL-8, macrophage inflammatory protein (MIP)-1α and MIP-1β, are elevated after a marathon (Ostrowski *et al.* 2001). In relation to exercise, IL-6 is produced in larger amounts than any other cytokine examined. Furthermore, it has been demonstrated that contracting skeletal muscles produce IL-6. The present review focuses on mechanisms underlying muscle-derived IL-6 and discusses for the first time possible biological roles of muscle-derived IL-6.

Characteristics of IL-6

IL-6 is a variably glycosylated protein with a molecular mass of 22–27 kDa, depending on the cellular source and the amount of post-translational modification. It is synthesized as a precursor protein of 212 amino acids, with a 28 amino acid signal sequence and a 184 amino acid mature segment (Haegeman *et al.* 1986; Hirano *et al.* 1986; May *et al.* 1986; Zilberstein *et al.* 1986). IL-6 is a member of a family of cytokines that includes leukaemia inhibitory factor, IL-11, ciliary neurotropic factor (CNTF), oncostatin M (OSM) and cardiotrophin-1 (CT-1) (Gadient & Patterson, 1999). Membership is based on similarities in helical protein structure and a shared receptor subunit (transmembrane glycoprotein (gp) 130) (Hirano *et al.* 1994; Hibi *et al.* 1996).

IL-6 has been classified as both a pro- and an anti-inflammatory cytokine, but the current view is that IL-6 has primarily anti-inflammatory effects. Infusion of IL-6 into humans results in fever but does not cause shock or capillary-leakage-like syndrome, as observed with the prototypical pro-inflammatory cytokines, IL-1 and TNFα (Rehman *et al.* 1997). Unlike IL-1 and TNFα, IL-6 does not upregulate major inflammatory mediators such as nitric oxide or matrix metalloproteinases. Rather, IL-6 appears to be the primary inducer of the hepatocyte-derived acute-phase proteins, many of which have anti-inflammatory properties. IL-6 directly inhibits the expression of TNFα and IL-1 and, furthermore, is a potent inducer of IL-1ra, which exerts anti-inflammatory activity by blocking IL-1 receptors, thereby preventing signal transduction of the pro-inflammatory IL-1 (Rehman *et al.* 1997).

IL-6 is produced by many different cell types, but the main sources *in vivo* are stimulated monocytes/macrophages, fibroblasts and vascular endothelial cells (Akira *et al.* 1993). Recently, however, much attention has been given to the striking observation that, during resting conditions, 10–35 % of the body's IL-6 is produced by adipose tissue (Mohamed-Ali *et al.* 1997).

Other cells known to express IL-6 include keratinocytes, osteoblasts, T cells, B cells, neutrophils, eosinophils, mast cells, smooth muscle cells and skeletal muscle cells (Akira *et al.* 1993). Typical stimuli for IL-6 production include IL-1, TNFα and bacterial endotoxin (Akira *et al.* 1993). Hypoxia induces IL-6 in cultured endothelial cells (Yan *et al.* 1995) and hypoxia *in vivo* elevates plasma IL-6 (Klausen *et al.* 1997).

IL-6 appears to play a central role in lipopolysaccharide (LPS)-induced fever (Sundgren-Andersson *et al.* 1998) and has growth-regulatory effects on a number of cells. Thus, IL-6 induces B and T cell differentiation and is involved in bone metabolism (Muraguchi *et al.* 1988; Houssiau *et al.* 1988; Takai *et al.* 1988).

Muscle damage and IL-6

Initially, it was thought that the cytokine response to exercise represented a reaction to exercise-induced muscle injury. Thus, we found that peak IL-6 concentrations were associated with prolonged muscle damage, using an eccentric exercise model in which the creatine kinase (CK) level peaked at day 4 after the exercise (Bruunsgaard *et al.* 1997). However, later studies from our group using exercise models in which CK peaked 1 day after exercise failed to show an association between peak IL-6 and peak CK levels (Ostrowski *et al.* 1998*a*, 1999). Furthermore, we have demonstrated recently, using an eccentric exercise model, that CK levels increased by up to 1000-fold with only a 4-fold increase in plasma IL-6 during the subsequent days (A. D. Toft, L. B. Jensen, H. Bruunsgaard, T. Ibfeldt, J. Halkjaer-Kristensen, M. A. Febbraio & B. K. Pedersen, unpublished data). The latter findings suggest that the huge increase in plasma levels of IL-6 in exercise models where the CK level does not change or is enhanced by a fewfold only, is related to mechanisms other than muscle damage. Also, a recent study (Croisier *et al.* 1999) failed to find an association between the increase in IL-6 and biochemical markers for muscle damage. These authors (Croisier *et al.* 1999) showed that training reduced the increase in myoglobin and decreased delayed-onset muscle soreness in response to a bout of eccentric exercise, whereas the increase in IL-6 was not influenced by training. It is most likely that the huge and immediate increase in IL-6 in response to long-duration exercise is independent of muscle damage, while muscle damage itself is followed by repair mechanisms including invasion of macrophages into the muscle leading to IL-6 production. IL-6 production in relation to muscle damage occurs later and is of smaller magnitude than IL-6 production related to muscle contractions. In a recent study, we tested the possibility that elevated levels of IL-6 during eccentric exercise might be inhibited by anti-oxidant treatment with vitamin C and vitamin E, which has been suggested to protect against muscle damage. However, we were unable to demonstrate any effect of anti-oxidants on plasma cytokines or muscle damage (Petersen *et al.* 2001). Non-steroid anti-inflammatory drugs might be used in future studies to evaluate the effect on IL-6, when the local inflammatory response is limited.

Kinetics of the IL-6 response to exercise

The finding of markedly increased levels of IL-6 after strenuous exercise has consistently been observed in many studies (Northoff & Berg, 1991; Sprenger *et al.* 1992; Ullum *et al.* 1994; Drenth *et al.* 1995; Nehlsen-Cannarella *et al.* 1997; Castell *et al.* 1997; Rohde *et al.* 1997; Hellsten *et al.* 1997; Ostrowski *et al.* 1998*a*, *b*, 1999; Toft *et al.* 2000). A 2-fold increase in plasma IL-6 was demonstrated after 6 min of intense exercise (Nielsen *et al.* 1996). In treadmill running, the IL-6 level in blood was significantly enhanced 30 min after the start, with peak levels being attained after 2.5 h of running (Ostrowski *et al.* 1998*a*). In other studies, in which IL-6 was not measured during the running exercise but at several time points afterwards, maximal IL-6 levels were found immediately after the exercise, followed by a rapid decline. Thus, following a marathon run maximal IL-6 levels (100-fold increase) were measured immediately after the 3–3.5 h race (Ostrowski *et al.* 1998*b*, 1999).

In contrast, using a prolonged eccentric one-legged exercise model lasting 1 h (Rohde *et al.* 1997) or a two-legged high-intensity eccentric exercise model lasting 30 min (Bruunsgaard *et al.* 1997), the IL-6 level did not peak until 1–1.5 h after the exercise. In another study, subjects performed five bouts of one-legged eccentric exercise. The concentration of plasma IL-6 peaked 90 min after the exercise and was elevated for 4 days (Hellsten *et al.* 1997). It is very clear that the kinetics of the IL-6 response differ between that induced by concentric muscle contractions and that induced by eccentric exercise associated with muscle damage (Bruunsgaard *et al.* 1997; Rohde *et al.* 1997; Ostrowski *et al.* 1998*b*, 1999). In relation to concentric exercise, the increase in IL-6 is tightly related to the duration of the exercise (Ostrowski *et al.* 1998*a*), and there appears to be a logarithmic relationship between the increase in IL-6 and the duration of the exercise. IL-6 levels decline after the concentric exercise to reach pre-exercise values within a few hours. In contrast, eccentric exercise induces only a modest increase in plasma IL-6 and the IL-6 level peaks some time after cessation of the exercise and is elevated for several days.

Intensity of exercise and IL-6

Data from the Copenhagen Marathon race (1996, 1997 and 1998, $n = 56$) suggest that there is a correlation between the intensity of exercise and the increase in plasma IL-6 (Ostrowski *et al.* 2001). Furthermore, a correlation between peak IL-6 and heart rate was demonstrated (Ostrowski *et al.* 1998*a*). Results from an animal study suggested that the increase in adrenaline during stress was responsible for the increase in IL-6 (DeRijk *et al.* 1994). However, recent data from our group showed that when adrenaline was infused into volunteers to closely mimic the increase in plasma adrenaline during 2.5 h of running exercise, plasma IL-6 increased only 4-fold during the infusion, but 30-fold during the exercise (Steensberg *et al.* 2001*b*). Thus, it seems that adrenaline only plays a minor role in the exercise-induced increase in plasma IL-6. It has been demonstrated previously that peak plasma IL-6 during exercise correlated with plasma lactate (Ostrowski *et al.* 1998*a*). However, in a recent study

(Steensberg *et al.* 2001*c*), patients with mitochondrial myopathy, characterized by high plasma levels of lactate, were examined. They were treated with dichloracetate (DCA) for 15 days. DCA inhibits pyruvate dehydrogenase kinase, thereby increasing the activity of the pyruvate dehydrogenase complex. The same exercise test was repeated on days with and without treatment. DCA lowered the plasma lactate and increased plasma IL-6 at rest. Furthermore, IL-6 increased in response to exercise only during DCA treatment. Thus, IL-6 production is not a direct result of high lactate levels.

Muscle-derived IL-6

A study was performed to test the hypothesis that inflammatory cytokines are produced in skeletal muscle in response to intense long-duration exercise (Ostrowski *et al.* 1998*b*). Muscle biopsies and blood samples were taken before and after a marathon race. The levels of IL-6 and IL-1ra proteins were markedly increased after the exercise. The plasma levels of IL-6 decreased, whereas those of IL-1ra increased further, 2 h after the exercise. A comparative polymerase chain reaction (PCR) technique was established to detect mRNA for cytokines in skeletal muscle biopsies and blood mononuclear cells (BMNCs). Before exercise, IL-6 mRNA could not be detected in muscle or BMNCs. In contrast, IL-6 mRNA was detected in muscle biopsies after exercise but not in the BMNC samples.

Starkie *et al.* (2000, 2001*b*) observed that the intracellular levels of IL-6 and IL-1ra protein in circulating monocytes were not augmented in response to exercise, and concluded that these cells did not contribute to the exercise-induced increases in plasma IL-6. The finding that blood cells do not contribute to the exercise-induced increase in IL-1β and IL-6 plasma levels was further substantiated using a quantitative PCR approach. Quantification of the IL-1β and IL-6 mRNA levels in BMNCs during exercise demonstrated no change despite an increase in the plasma level of the proteins (Moldoveanu *et al.* 2000). Recently, we measured IL-1β and IL-6 mRNA levels in muscle biopsies using quantitative competitive RT-PCR and found that both specific mRNAs increased more than 10-fold following a marathon (Schjerling *et al.* 2001). The finding of IL-6 mRNA in muscle in response to exercise was confirmed in a rat exercise model, using the quantitative competitive RT-PCR method (Jonsdottir *et al.* 2000). In this model, rats were subjected to electrically stimulated eccentric or concentric contractions of one hind leg, while the other leg remained at rest. The eccentric and concentric contractions both resulted in elevated levels of IL-6 mRNA in the exercised muscle, whereas the level in the resting leg was not elevated. The finding of similar levels of IL-6 mRNA in both concentric- and eccentric-exercised muscle indicates that the cytokine production cannot be as closely related to muscle damage as was first thought. It does, however, appear that the local IL-6 production is connected with exercising muscle – and is not due to a systemic effect – because IL-6 mRNA was elevated only in the muscle from the exercised leg, and not in the other resting leg.

Recently, we demonstrated that the net IL-6 release from contracting skeletal muscles could more than account for the exercise-induced increase in arterial plasma concentrations (Steensberg *et al.* 2000). Moreover, by obtaining arterial-femoral venous differences from an exercising leg, we found that exercising muscles released IL-6. In addition, during the last 2 h of exercise the release per unit time was ~17-fold higher than the amount accumulating in the plasma. Although IL-6 appears to be produced in the muscle, which cell types within the muscle are responsible for the production remains unknown. Myoblasts have been shown to be able to produce IL-6 (Bartoccioni *et al.* 1994; De Rossi *et al.* 2000), but endothelial cells (Yan *et al.* 1995), fibroblasts (De Rossi *et al.* 2000) and smooth muscle (Klouche *et al.* 1999) have also been shown to produce IL-6 under certain conditions. *In situ* hybridization for IL-6 mRNA in mouse hearts after LPS stimulation gave a low signal from cardiomyocytes but a greater signal from non-myocyte cells (Saito *et al.* 2000). *In situ* hybridization on damaged muscles showed increased expression of IL-6 mRNA inside muscle fibres as well as in mononucleated cells (Kami & Senba, 1998).

Carbohydrate ingestion and IL-6

Several studies have reported that carbohydrate ingestion attenuates elevations in plasma IL-6 during both running and cycling (Nehlsen-Cannarella *et al.* 1997; Nieman *et al.* 1998). In contrast, researchers from Melbourne, Australia (Starkie *et al.* 2000) reported that plasma IL-6 was unaffected by carbohydrate ingestion during cycling. However, in that study the subjects were highly endurance trained and plasma IL-6 increased to only ~2 pg ml^{-1}, even without carbohydrate ingestion. This increase is markedly less than that previously observed in moderately trained subjects (Nieman *et al.* 1998). Recently, the same group reported that carbohydrate ingestion did attenuate the increase in plasma IL-6 found in response to both cycling and running (Starkie *et al.* 2001*a*). In the latter experiment, subjects of similar aerobic fitness to those previously reported were used (Nieman *et al.* 1998). Furthermore, IL-6 gene expression in the muscles was investigated. However, the level of IL-6 mRNA was found not to be affected by carbohydrate ingestion. IL-6 protein release from contracting muscle was not measured, and it is possible that carbohydrate ingestion did affect the release of IL-6, without altering the gene expression.

These authors suggested that it is the liver rather than contracting muscles that is responsible for the differences in plasma IL-6 between the carbohydrate and the non-carbohydrate trial. Moreover, it is possible that carbohydrate ingestion may have blunted IL-6

production in hepatic tissue. In addition, differences in the clearance of IL-6 may be responsible for the attenuated plasma IL-6 during carbohydrate ingestion. Further investigation is needed to clarify whether organs other than contracting muscles are involved in IL-6 production during exercise.

Muscle derived IL-6 may act as a hormone

During the past 30 years, there has been intensive research to unravel the mechanisms that regulate the release of glucose from the liver to the blood during physical exercise, so that the blood glucose level is maintained in spite of increased glucose uptake in working skeletal muscles (Kjaer, 2001). Research has demonstrated that exercise-induced changes in insulin and/or glucagons (Kjaer, 2001), cortisol (Cryer, 1993), adrenaline (Howlett *et al.* 1999) or adrenergic neural stimulation (Sigal *et al.* 1994, 2000) cannot, by themselves, account for the exercise-induced increase in hepatic glucose production. Indeed, it has been concluded that the possibility exists that an as yet unidentified factor, released from contracting muscle cells, may contribute to the increase in hepatic glucose production (Howlett *et al.* 1999).

An elevated plasma IL-6 response was found when subjects exercised in a glycogen-depleted state (Gleeson & Bishop, 2000). Recently, we presented data showing that release of IL-6 from a glycogen-depleted exercising leg occurred 1 h before release was observed in a non-depleted control leg (Keller *et al.* 2001; Steensberg *et al.* 2001*a*). Furthermore, when individual data with regard to the legs with the lowest glycogen content at the end of exercise were analysed, it was demonstrated that the highest levels of IL-6 mRNA were expressed in these legs. Therefore, the glycogen content or an energy crisis in the contracting muscle may be one stimulus for the IL-6 release. IL-6 has been shown to have a marked influence on hepatic glucose metabolism. Moreover, IL-6 has also been shown to inhibit glycogen synthase activity and accelerate glycogen phosphorylase activity (Kanemaki *et al.* 1998). In addition, it has been demonstrated that injection of recombinant human IL-6 (rhIL-6) into humans increases hepatic glucose production (Stouthard *et al.* 1995) and the fasting blood glucose concentration in a dose-dependent manner (Tsigos *et al.* 1997). These data raise the possibility that the IL-6 produced by contracting skeletal muscle partly mediates the hepatic glucose output necessary to maintain blood glucose homeostasis when the uptake of blood glucose by skeletal muscles is increased by prolonged exercise (Fig. 1).

Besides the glucoregulatory effect of IL-6, this cytokine may also be involved in other metabolic pathways (Fig. 1). Concomitantly with the increase in liver glucose output during IL-6 infusion, Stouthard *et al.* (1996) observed an increased release of free fatty acids (FFAs). Furthermore, infusion of IL-6 into rats increased serum triglyceride and FFA levels in a dose-dependent manner (Nonogaki *et al.* 1995). The hypertriglyceridaemia was due to increased secretion by the liver and not to decreased clearance. The increased levels of serum FFAs were due to lipolysis.

Increased glucose transport was found in jejunal tissue incubated with IL-6, compared with controls (Hardin *et al.* 2000). Moreover, IL-6 also appears to be able to increase the absorption of glucose in the gut, thereby increasing the plasma glucose levels. Furthermore, there is evidence to suggest that IL-6 may augment glucose uptake by insulin-sensitive tissues. Stouthard *et al.* (1996) demonstrated that infusion of rhIL-6 into human subjects increased whole body glucose disposal and subsequent oxidation compared with a control trial. Even though endogenous glucose production was increased with rhIL-6 infusion, the metabolic clearance rate of glucose was higher in this trial, suggesting that relative hyperglycaemia was not responsible for the augmented glucose disposal. Moreover, in a follow-up study, it was demonstrated that IL-6 increased both basal and insulin-stimulated glucose uptake in cultured 3T3-L1 adipocytes (Stouthard *et al.* 1996). These authors concluded that IL-6 acted by increasing glucose transporter (GLUT)-1, intrinsic activity. Although highly speculative, it is possible that IL-6 produced by the muscle may act on signalling molecules, which enhance translocation of GLUT-4, the transporter responsible for facilitating contraction-mediated glucose uptake.

It is tempting to speculate that IL-6 may be involved in glucoregulatory processes in circumstances in which glucose homeostasis is disrupted. Basal serum IL-6 is higher in type II diabetics (Pickup *et al.* 2000) and in cancer patients with insulin resistance (Makino *et al.* 1998), while a polymorphism of the IL-6 gene influences insulin sensitivity in humans (Fernandez-Real *et al.* 2000). Interestingly, in the study by Pickup *et al.* (2000) the basal production of IL-6 in cultured blood cells from diabetics was depressed compared with blood from non-diabetics. Therefore, the possibility exists that the elevated serum IL-6 is a consequence of an increased production and release of IL-6 from insulin-sensitive tissue in response to the impaired insulin sensitivity. Based on this information, it is of utmost interest to investigate the role of muscle-derived IL-6 for metabolic homeostasis, including substrate uptake and release in different tissues.

Does IL-6 have a local effect on the muscle tissue?

Another role for the exercise-produced IL-6 may be to regulate processes within the producing muscles (Fig. 1). IL-6 is known to have local regulatory functions in other tissues such as the nervous system (Van Wagoner & Benveniste, 1999) and the skeleton (Franchimont *et al.* 1997).

The downstream signalling pathway for IL-6 has been well investigated, especially in liver cells. IL-6 belongs to a family of cytokines which bind to different specific

receptors but which all transmit signals over the cell membrane via the gp130 tyrosine kinase receptor. IL-6 binds to the IL-6 receptor on the surface of target cells, which then causes dimerization of the tyrosine kinase receptor gp130. Upon dimerization, gp130 recruits cytoplasmic Janus kinases (JAKs), which then phosphorylate signal transducer and activator of transcription 3 (STAT3). The phosphorylated STAT3 then dimerize and translocate from the cytoplasm into the nucleus where STAT3 activates transcription of a number of different genes. Besides the more specific signal transduction pathway via STAT3, the dimerization of gp130 also causes activation of the phosphatidylinositol-3 kinase (PI-3 kinase) and the mitogen-activated protein kinase (MAPK) cascade. An important review on the gp130 signal transduction pathway is given by Hirano *et al.* (1997). gp130 is ubiquitously expressed throughout the body (Hibi *et al.* 1990; Saito *et al.* 1992), whereas the distribution of the IL-6 receptor is more restricted. IL-6 receptor mRNA is found in skeletal muscle, although at low levels, but the level is subject to inducing signals as demonstrated by LPS stimulation (Zhang *et al.* 2000). However, muscles do not necessarily need to express the IL-6 receptor, since serum contains a soluble form of the receptor which can substitute for the membrane-bound receptor (Croucher *et al.* 1999). What then could be the possible function of a local IL-6 signal? Myoblast proliferation is stimulated by IL-6 and satellite cell proliferation is regulated by an autocrine secretion of IL-6 (Austin & Burgess 1991; Austin *et al.* 1992; Cantini *et al.* 1995). Furthermore, IL-6 administration also enhances differentiation of the myoblasts (Okazaki *et al.* 1996). This has led to the idea that IL-6 may be involved in hypertrophy during resistance exercise (Vierck *et al.* 2000). However, IL-6 production from the muscles is mainly seen after endurance exercise rather than after resistance exercise (Ostrowski *et al.* 2000). Overexpression of IL-6 in transgenic mice causes muscle atrophy and increased levels of cathepsins in muscle, indicating that IL-6 is involved in regulating muscle protein breakdown (Tsujinaka *et al.* 1995). This atrophy was completely abolished following injection of antibodies against the IL-6 receptor (Tsujinaka *et al.* 1996). However, this effect on muscles is not necessarily a direct effect, since for instance the circulating level of insulin-like growth factor 1 (IGF-1) also decreased in the IL-6 transgenic mice (De Benedetti *et al.* 1997). IL-6 can induce the expression of vascular endothelial growth factor (VEGF) (Cohen *et al.* 1996) and could therefore be responsible for the upregulation of VEGF seen after exercise (Gustafsson *et*

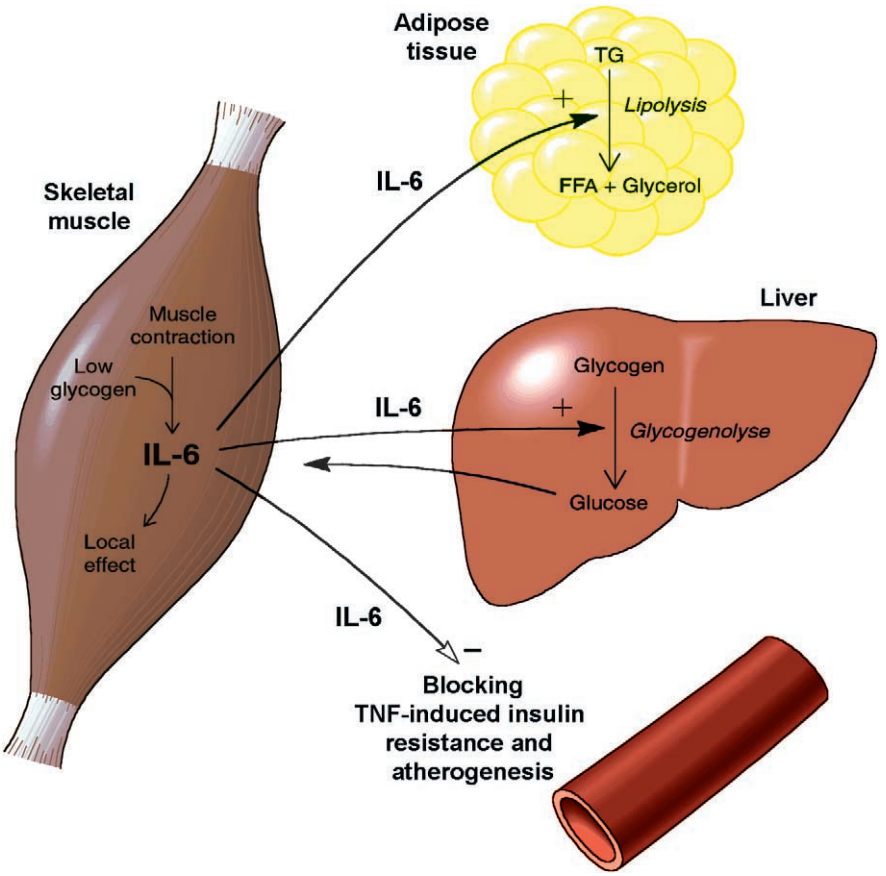

Figure 1

Schematic presentation of the possible biological effects of muscle-derived IL-6. TG, triglyceride; FFA, free fatty acid.

al. 1999), suggesting a role in capillary growth. Since systemic IL-6 has well-known effects on glucose metabolism in the liver and fatty acid metabolism in the adipose tissue as described above, another potential function of local IL-6 may well be to regulate the metabolism within the muscle by exerting similar or perhaps opposite effects on the muscle tissue. The actual local role of exercise-produced IL-6 in muscle has still to be determined.

How does muscle-derived IL-6 interact with IL-6 produced by inflammatory cells or adipose tissue?

Given the many beneficial effects of physical exercise on health, it is hard to believe that muscle-derived IL-6 is detrimental to health. However, elevated levels of circulating IL-6 have been associated with several disorders. Thus, increased levels of TNF and IL-6 have been observed in obese individuals, in smokers and in non-insulin-dependent diabetes mellitus (Vgontzas *et al.* 2000). In several population-based studies, plasma concentrations of IL-6 have been shown to predict total and cardiovascular mortality (Ridker *et al.* 2000*a*, *b*). Furthermore, ageing is associated with increased levels of both TNFα and IL-6 (Bruunsgaard *et al.* 1999). It has been proposed that IL-6 is the mediator that links the acute phase response to visceral obesity, insulin resistance and atherosclerosis (Yudkin *et al.* 2000; and Dr Robert S. Munford's Grand Rounds of July 6, 2000).

High levels of IL-6 in patients with metabolic syndrome may be explained by the fact that IL-6 is produced in adipose tissue (Mohamed-Ali *et al.* 1997; Fried *et al.* 1998). Omental adipose tissue produces more IL-6 than subcutaneous tissue (Fried *et al.* 1998). Adipose tissue also produces and releases TNFα (Tsigos *et al.* 1999), and TNFα is thought to play a mechanistic role in insulin resistance. Thus, TNFα downregulates GLUT-4 and inhibits insulin receptor activity (Hotamisligil, 1999). Since TNFα can trigger IL-6 release, one theory holds that it is adipose tissue TNFα that is actually the 'driver' behind the metabolic syndrome. In support of this theory is the finding that in elderly people serum levels of leptin and TNFα were correlated even after the effect of sex and body mass index was taken into account (Bruunsgaard *et al.* 2000*a*, *b*). It was also demonstrated that blood levels of soluble TNFα receptors (an indicator of TNF activation) correlate with blood leptin levels in both controls and diabetic subjects (Mantzoros *et al.* 1997). Furthermore, TNFα was elevated in elderly patients with atherosclerosis compared with age-matched subjects without this diagnosis (Bruunsgaard *et al.* 1999, 2000*a*, *b*). However, although TNFα correlated with IL-6 (Bruunsgaard *et al.* 1999), the latter cytokine was not associated with atherosclerosis. In addition, TNFα is the prototype of a pro-inflammatory cytokine, whereas IL-6 is now regarded as an anti-inflammatory cytokine. Thus, it is possible that TNFα, rather than IL-6, should be regarded as the cytokine that induces insulin resistance and thereby initiates diabetes type 2 and atherosclerosis. According to this theory, muscle-derived IL-6 may work to inhibit the effects of TNFα and IL-6 may represent an important messenger from muscle work to health effects (Fig. 1). An alternative explanation is that muscle-derived IL-6 represents an isoform that differs from the IL-6 molecules produced by adipose tissue and inflammatory cells.

Conclusion

Muscle-derived IL-6 is released into the circulation in large amounts and is likely to work in a hormone-like fashion, exerting its effect on the liver and adipose tissue, thereby contributing to the maintenance of glucose homeostasis during exercise and mediating exercise-induced lipolysis. Muscle-derived IL-6 may also work to inhibit the effects of pro-inflammatory cytokines such as TNFα, thereby protecting against insulin resistance and atherogenesis.

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